Jun-ichi
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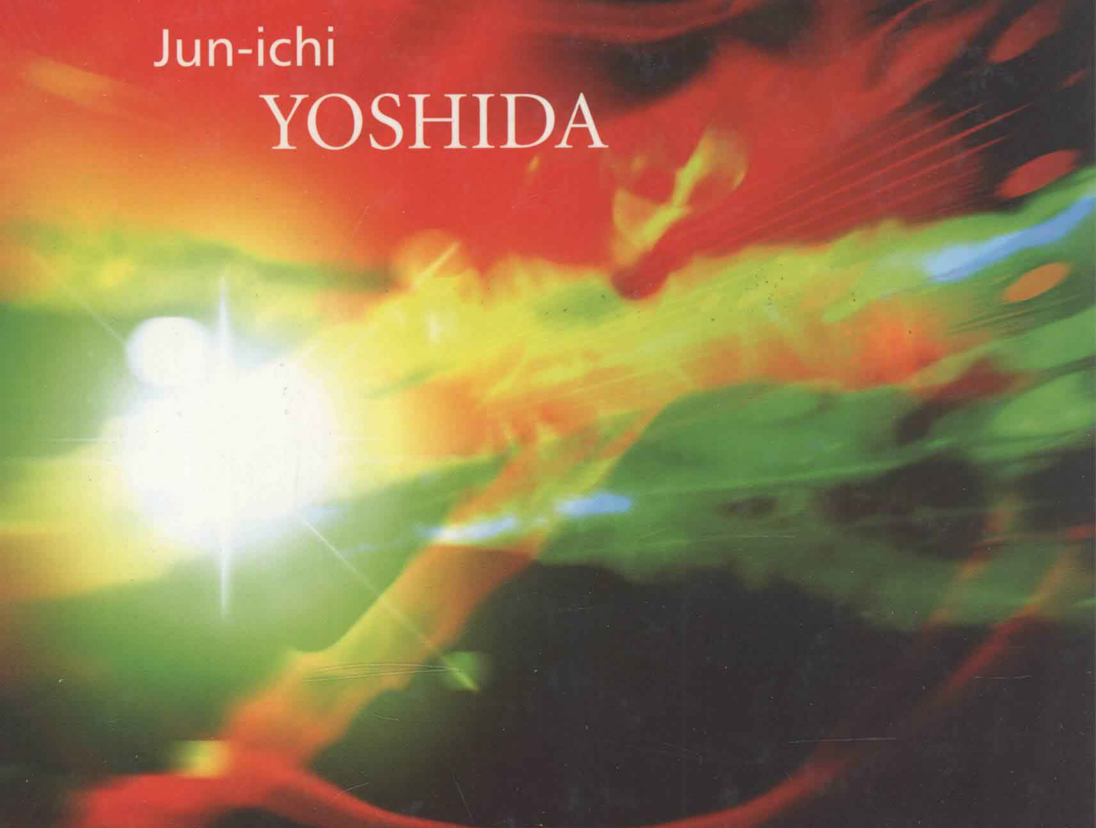

FLASH CHEMISTRY

Fast Organic Synthesis in Microsystems

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Flash Chemistry

Fast Organic Synthesis in Microsystems

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Flash Chemistry

Preface

The main objective of this book is to provide, in a concise form, a current overall picture of flash chemistry; background, principles, devices, and applications in organic and polymer synthesis. Because of space limitations our discussion in this book is not an exhaustive compilation of all known examples. Rather, it is a sampling of sufficient variety to illustrate the concept and the scope of flash chemistry. I usually focus on the works that have been done in my group as examples because I know them in more detail than other works reported in the literature. I hope that these examples and the accompanying discussions will serve as a guide to the potential of flash chemistry.

I thank the members of my research group, especially Prof. Seiji Suga and Dr. Aiichiro Nagaki, and the members of the NEDO (New Energy and Industrial Technology Development Organization, Japan) projects, who did extensive work that is demonstrated in this book. I also acknowledge many discussions over the years with the members of GRAMS (Groups for Research on Automated Flow and Microreactor Synthesis) in Kinki Chemical Society, especially Prof. Ilhyong Ryu, and the members of the international research community of microreactor synthesis, especially Prof. Holger Löwe, Prof. Volker Hessel, Dr. Jürgen J. Brandner, Prof. Shinji Hasebe, and Prof. Kazuhiro Mae.

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Jun-ichi Yoshida

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Introduction

We tend to think that what we usually do is appropriate. This is often true in our daily life. However, it is not necessarily true in the field of science. For example, we usually run reactions in a centimeter size flask in an organic chemistry laboratory. Why? The reason is probably, that the sizes of the flasks are similar to the size of our hands. However, the sizes of the flasks are not necessarily appropriate from a molecular-level viewpoint. Flasks are often too big for the control of molecular reactions. Scientifically, smaller reactors such as microreactors provide a much better molecular environment for reactions. What about reaction times? Reactions in laboratory synthesis usually take minutes to hours to obtain a product in a sufficient amount. Why? It is probably because a time interval of minutes to hours is acceptable and convenient for human beings. In such a range of time, we can recognize how the reaction proceeds. We start a reaction, wait for a while, and stop it in this range of time. If reactions are too fast, it is difficult to determine how the reaction proceeds, because the reaction is complete too soon after it is started. Therefore, we have chosen reactions that complete in a range of minutes to hours. Another reason is that we are able to conduct only such reactions that require minutes to hours for completion in a controlled way. In other words, in laboratory synthesis, we cannot conduct faster reactions that complete within milliseconds to seconds, because they are too fast to control. In such cases, significant amounts of unexpected compounds are obtained as byproducts. In addition, extremely fast reactions sometimes lead to explosions. However, we should keep in mind that such limitations of reaction

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time for chemical synthesis are only applicable for flask chemistry that we usually do in a laboratory.

1.1 FLASK CHEMISTRY

Based on conventional flask chemistry, organic synthesis has witnessed a steady march in the progress of our understanding of factors governing chemical reactions. With a rational design of synthesis, desired compounds are produced in a highly selective manner. The role of organic synthesis has been extended to various fields of science and technology, such as materials, pharmacy, and medicine. Conventional organic synthesis, however, has been a rather time-consuming task; chemists have been using slow reactions because fast reactions are difficult to control and often give significant amounts of undesired by-products, as stated above. Reaction times in conventional organic synthesis usually range from minutes to hours. The rapid progress in science and technology based on organic compounds means the demand to produce desired compounds in a highly time-efficient way has been increasing. To meet such demands and to achieve rapid synthesis of a variety of organic compounds, acceleration of organic synthesis is highly desirable. For this purpose, flash chemistry, where much faster reactions are conducted in a controlled and selective way to produce desired products, is greatly needed.

We are still running chemical reactions using much of the same apparatus that was used in the eighteenth and nineteenth centuries (Figure 1.1). The sizes of the flasks are determined not by any scientific

Figure 1.1 Ugo Schiff (1834–1915) (provided by the University of Florence)

reasons but probably by the size of our hands. It is not necessary to use reactors of flask size for studies of chemical reactions and synthesis of compounds. Therefore, if we free ourselves from the constraints of flask chemistry, we can expect to have the chance to conduct much faster reactions in a highly controlled and selective way to synthesize desired compounds. There should be many fast reactions that we have not yet explored because of the constraints of the reaction environment. Such constraints should be removed to further develop the efficiency and utility of organic synthesis. In order to do this, we need microflow systems as a new environment for chemical reactions.

1.2 FLASH CHEMISTRY

The word ‘flash’ is not new in the history of chemistry. Flash chromatography[1] is one of the fundamental techniques for separating organic compounds in laboratory synthesis. In fact, flash chromatography is very popular with organic chemists as a convenient and effective method for separation in daily laboratory work. For synthesis, flash vacuum pyrolysis[2] is also a well-known technique that has been available for many years. Flash laser photolysis[3] is widely used for mechanistic studies because it serves as a powerful method for generating reactive species in a very short period of time. However, flash laser photolysis does not seem to be suitable for chemical synthesis because it is rather difficult to produce a large amount of compounds using this technique. In the ‘flash chemistry’ proposed here, a substrate undergoes extremely fast reactions to give a desired product very quickly in a highly selective manner. Reaction times rage from milliseconds to seconds (Figure 1.2). Because flash chemistry

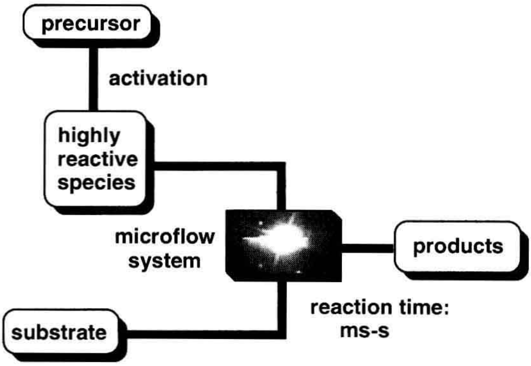

Figure 1.2 Schematic diagram of flash chemistry

uses a continuous flow system, it is fairly easy to make a larger quantity of compounds than one can expect from the size of the reactor. In any case, the word 'flash' is very common in chemistry, but the term 'flash chemistry' is uncommon.

It is important to propose new words for the developments in new fields of science and technology; as Wittgenstein wrote in his book:[4] 'A new word is like a fresh seed thrown on the ground of the discussion'. A Japanese poet, Toson Shimazaki, also wrote in the preface of his collection of poems:[5] 'A new word leads to a new life'. Therefore, it seems useful and productive to introduce the expression 'flash chemistry'.

1.3 FLASK CHEMISTRY OR FLASH CHEMISTRY

At the molecular level, chemical reactions take place in the range of 10^{-13}–10^{-12} s (see Chapter 2), while reaction times range from minutes to hours (10^2–10^5 s) in a flask (Figure 1.3). The size of molecules is in the range of 10^{-10}–10^{-8} m, whereas the size of a flask ranges from 10^{-2} to 10^0 m. So, there is a rough correlation between the reaction time and the size of the reaction environment, as shown in Figure 1.3. In flash chemistry, we use a reactor, the size of which ranges from 10^{-6} to 10^{-3} m. The

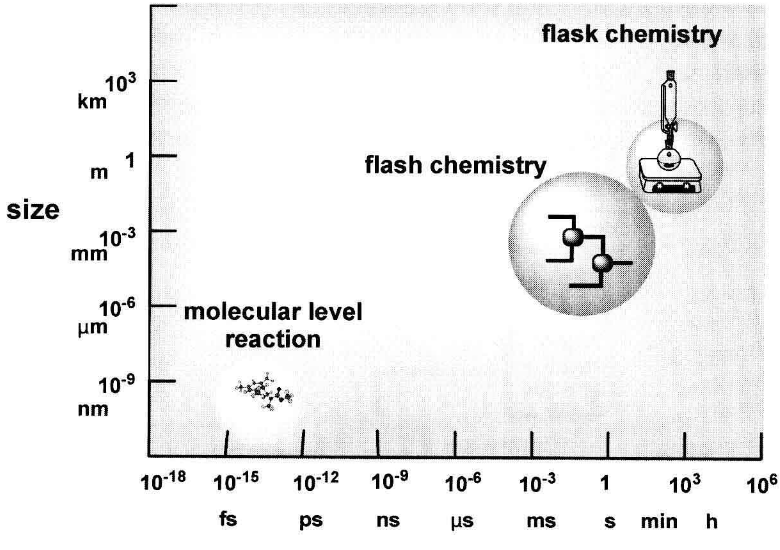

Figure 1.3 Time–space relationship for chemical reactions

reaction time ranges from 10^{-3} to 1 s. Therefore, it is easy to understand that the size of the reaction environment of flash chemistry is closer to the size of the molecular level reaction environment than is that of flask chemistry.

This book provides an outline of the concept of flash chemistry for conducting extremely fast reactions in a highly controlled manner using microflow systems. In the following chapters, we will discuss the background, the principles, and applications of flash chemistry.

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2

The Background to Flash Chemistry

2.1 HOW DO CHEMICAL REACTIONS TAKE PLACE?

What is a chemical reaction? How does it take place? These questions are the most fundamental questions of chemistry, and they are the last to be solved. In order to deal with flash chemistry, however, let us begin with a consideration of such fundamental questions.

When we consider a chemical reaction, there are two viewpoints; a macroscopic one and a molecular level one. It was only about a hundred years ago when the reality of molecules was established. In 1905, Einstein proposed a theory of Brownian motion, and later (1908–1912) Perrin proved it by experimental work. They showed that Brownian motion is caused by the collision of molecules on small particles (micrometer size). Although some scientists at the time considered that molecules only had a virtual existence that was useful to explain chemical phenomena, since then, no scientist has doubted the existence of molecules. Since that time a molecular point of view has become very popular in chemistry, although it is rather difficult to see molecules directly even with the present technology.

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